State of the Art Management of Pancreatic Cancer

Laleh Melstrom, MD, MS, FACS
DISCLOSURE

- Nothing to disclose
Demographics/Risk Factors/Presentation

• Epidemiology\textsuperscript{1}:
  – 8\textsuperscript{th} most common malignancy
  – 4\textsuperscript{th} leading cause of adult cancer deaths
  – \textbf{2017}-53,670 new cases and 43,090 deaths
  – Lifetime Risk: 1 in 65 (1.5%)
  – Average Age: 72 yo
    • 90% are >55 yo; 70%>65 yo
• Risk Factors: Smoking (2-3x), DM, chronic pancreatitis, familial syndromes
• Most common signs/symptoms: jaundice, weight loss, abdominal pain, malnutrition, new DM diagnosis
Outline & Objectives

- Establishing a Diagnosis: pancreatic mass
- Assessing Resectability and Staging
- Technical Aspects of Resection and Reconstruction
- Adjuvant Therapy after Resection
- Management of Metastatic Disease
- Palliation
- Future Therapies in development.
Initial imaging presentation: Tumor location

Pancreatic Head

Uncinate

Pancreatic Body

Pancreatic Tail
Establishing a Diagnosis & Staging

- Imaging: Triphasic CT of the chest/abdomen/pelvis, MRI with contrast, MRCP
- Tissue Diagnosis by EUS, IR guided FNA
- Sometimes not possible
- Distal bile duct strictures: 80% are malignant—either duodenal, ampullary, bile duct or pancreas

- CEA, CA19-9, CBC, PT/INR, CMP
Assessing Resectability

Pancreatic Head

Arterial Involvement

Venous Involvement

<180°  >180°  +Deformity

<180°  >180°+Deformity  >180°+Deformity
# Radiographic Classification: Borderline Resectable Cancer

<table>
<thead>
<tr>
<th>Pancreatic Head/Uncinate Process</th>
<th>NCCN</th>
<th>AHPBA/SSAT/SSO</th>
<th>MD Anderson</th>
<th>Alliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV/PV</td>
<td>Tumor Contact &gt; 180</td>
<td>Tumor abutment with/without impingement, encasement of SMV/portal without arterial encasement, short segment occlusion, able to reconstruct</td>
<td>Short-segment occlusion with suitable vessel for reconstruction</td>
<td>Tumor-vessel interface ≥ 180 and/or reconstructable occlusion</td>
</tr>
<tr>
<td>Contact ≤ 180, with contour irregularity or thrombosis</td>
<td>Suitable vessel for reconstruction</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SMA</td>
<td>Solid contact ≤ 180</td>
<td>Abutment not to exceed 180</td>
<td>Tumor abutment ≤ 180</td>
<td>Tumor-vessel interface &lt; 180</td>
</tr>
<tr>
<td>CHA</td>
<td>Short segment contact</td>
<td>GDA encasement up to hepatic artery, short segment encasement or direct abutment</td>
<td>Short-segment encasement/abutment of CHA</td>
<td>Reconstructable short segment interface of any degree</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pancreatic Body/Tail</th>
<th>NCCN</th>
<th>AHPBA/SSAT/SSO</th>
<th>MD Anderson</th>
<th>Alliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac Axis</td>
<td>Solid tumor contact ≤ 180</td>
<td>Same as NCCN</td>
<td>Same as NCCN</td>
<td>Tumor-vessel interface &lt; 180</td>
</tr>
<tr>
<td>Solid tumor contact &gt; 180, without aortic involvement, uninvolved GDA</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Notes:** NCCN, National Comprehensive Cancer Network; AHPBA/SSAT/SSO, Americas Hepatopancreatobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology; SMV/PV, Superior mesenteric vein/portal vein; SMA, Superior mesenteric artery; CHA, Common hepatic artery; GDA, gastroduodenal artery.
Endoscopic Ultrasound and ERCP

- **EUS**: Tissue diagnosis, vascular involvement – operator dependent
- **ERCP**: brushings, bile duct stenting

- PLEASE CONSIDER ASKING SURGICAL OPINION PRIOR TO INSTRUMENTATION
**Peri-operative: Biliary Stents**

**Plastic Stents**

- Composition: polyethylene, polyurethane, or Teflon
- Stent diameter: 5F to 12F
- Stent length: 1 to 18 cm
- Placement:
  - Stents that are 10F require an endoscope with a 3.7-mm accessory channel
  - Larger stents (11.5F and larger) require a 4.2-mm channel.
- Configurations:
  - Classic
  - Single or double pigtail
  - Flanged
- Radio-opaque
Self-expanding Metal Stents

- Composition: Nitinol (metal alloy)
  - Ideal radial expansile force without sacrificing flexibility
- Stent diameter: 6 to 10mm when expanded
- Stent length: 4 to 12cm
- Placement:
  - Constrained by outer-sheath 8.5 Fr or smaller
  - Constrained by a tightly wound filament
- Configurations:
  - Covered
  - Partially covered
  - Uncovered
- Radio-opaque
- Uncovered stents difficult to remove
**Efficacy Considerations**

- Patency: > 10Fr better than <10Fr
- Occlusion of >10Fr stents occurs at 3-6 months
- SEMS have much longer patency
- Plastic Stents are more cost effective in patients with life expectancy <4 months
  - Occlusion rates 30-40% by 4 months

- Covered metal stents have significantly greater stent patency by more than 60 days compared to uncovered SEMS

- Covered SEMSs had higher stent migration, tumor overgrowth, and sludge formation
Safety Considerations

- **Migration: Obstruction, Perforation or Fistula**
  - Plastic: 5-10%
  - Covered SEMS: 3-12%
  - Uncovered: <1%

- **Pancreatitis**
  - Plastic < Uncovered SEMS = Covered SEMS
  - Sphincterotomy reduces pancreatitis

- **Cholecystitis:**
  - Covered SEMS ~10% if placed across cystic duct

- **Cholangitis:**
  - Related to occlusions
  - Highest with Plastic Stents
**Peri-operative: Biliary Stents**

Which one to use?

- **Inoperable Cancer**
  - Life Expectancy <4 months: Plastic Stent >10Fr
  - Life Expectance >4 months: SEMS Uncovered or Covered

- **Borderline Resectable or Plan for Neoadjuvant**
  - Short partially covered or uncovered SEMS
  - Covered SEMS

- **Occluded Covered Stent**
  - Covered SEMS
PET-PANC: Multi-centre prospective diagnostic accuracy and clinical value trial of FDG PET/CT in the diagnosis and management of suspected pancreatic cancer.

- 2011-13: 589 patients suspected of having pancreatic cancer
- MDCT vs FDG PET/CT
- Sensitivity 92.7% PET vs 88.5% CT
- Specificity 75.8% PET vs 70.6% CT
- Influenced management in 250 (45%)
- Stopped futile surgery in 58 (20%)
Surgery vs ChemoRT in Localized Disease

• **Design**
  - Locally advanced resectable cancer without arterial involvement randomized to segmental resection or chemoRT (continuous 5FU + 50 Gy)
  - Multi-institutional, 42 patients
  - Endpoint: OS

• **Results at 5 year followup**
  - Surgery group with improved
    - 1 year survival (62% vs 35%, p<0.05)
    - 3 year survival (20% vs 0%, p<0.05)
    - Mean survival (10.8 vs 22.6 mo, p<0.05)

• **Conclusions**
  - Surgical resection is the treatment of choice
Technical Aspects: Distal Pancreatectomy and Splenectomy

- Often start with diagnostic laparoscopy—yield about 10%, higher in pancreas tail lesions and with CA 19-9 >150.
- Small midline incision
- Inspect/Palpate abdomen
- Mobilize stomach
- Ligate divide splenic artery
- Divide pancreas
- Leave a drain at the cut edge
Robotic Distal Pancreatectomy and Splenectomy
Technical Aspects of Resection and Reconstruction

- Allen O. Whipple MD
- First Whipple in 1935 at the Memorial Hospital (now MSKCC)
- Refined it to one stage operation in 1940
Technical Aspects of Resection and Reconstruction: Whipple-pancreaticoduodenectomy

- Often start with diagnostic laparoscopy-yield about 10%, higher in pancreas tail lesions and with CA 19-9 >150.
- Small midline incision
- Inspect/Palpate abdomen
- Mobilize stomach
- Look at SMV at neck
Technical Aspects of Resection and Reconstruction

- If amenable to creating tunnel underneath pancreas neck
- Divide stomach – prepyloric or post pyloric duodenum
- Cholecystectomy,
- Divide Common hepatic duct
- Divide duodenum beyond ligament of Treitz
- Divide Pancreas Neck
- Divide uncinate off SMV/SMA

Illustration by Scott Weldon Baylor College of Medicine
Technical Aspects of Resection and Reconstruction
Randomized Trials that Work to Answer SOME important SURGICAL questions

- Pylorus Preserving Pancreaticoduodenectomy (PPPD) vs standard PD
- Extended Lymphadenectomy vs standard PD
- Anastomotic techniques
- Surgery in the setting of unresectable disease
- Postoperative Management
Pylorus preserving vs Standard Whipple: NO DIFFERENCE

**Design**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran et al.</td>
<td>170</td>
</tr>
<tr>
<td>Seiler et al.</td>
<td>214</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>36</td>
</tr>
</tbody>
</table>

**Results**

- No differences in:
  - Overall long-term and disease-free survival rates
  - Operating time
  - Blood loss
  - Hospital stay
  - Mortality and morbidity
  - Positive resection margins
  - Quality of life
  - Delayed gastric emptying (22-38%)

Tran et al. *Ann Surg* 2004;240: 738-45
Extended LND vs Standard PD: NO BENEFIT

**Design**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo et al.*</td>
<td>Standard PD/PPP vs extended PD</td>
<td>294</td>
</tr>
<tr>
<td>Farnell et al.</td>
<td>Standard PD vs PD with ELND</td>
<td>132</td>
</tr>
</tbody>
</table>

**Results**

- Extended lymphadenectomy*
  - Increased total LN resected (28 vs 17; p=0.001)
  - Higher complications rate (43% vs 23%; p=0.01)
  - Increased LOS (14.3 vs 11.3 days; p=0.003)
  - Increased rate of POPF (13% vs 6%; p=0.05)
  - Increased DGE (16% vs 6%; p=0.006)
  - Decreased early QOL
- No difference in OS
  - Over 200,000 patients would be needed to power a trial to detect a OS benefit

**Conclusions**

- No benefit with extended lymphadenectomy

Farnell et al. Surgery 2005;138:618-28
Pancreaticoenteric Reconstruction: Do what YOU do BEST

**Design**
- Patients undergoing PD in the setting of periampullary neoplasms with soft pancreas and PD diameter < 5 mm, randomized to PG or PJ
- Single institution, 151 patients
- Endpoint: Postoperative abdominal complications

**Results**
- No difference in postoperative complications (29% in PG vs 39% in PJ; P = NS) or mortality
  - No difference in POPF (13% in PG vs 16% in PJ; P = NS)
  - Significantly more biliary fistulas with PJ (8.5% vs 0%; P = 0.01), intraabdominal fluid collections (27% vs 10%; P = 0.01), and DGE (12% vs 3%; P = 0.03)

**Conclusions**
- PG and PJ can be performed with similar perioperative morbidity and mortality

Stapler Reinforcement

- **Design**
  - Patients undergoing distal pancreatectomy were randomized to stapler or hand-sewn closure of the pancreatic remnant
  - Multi-institutional, 450 patients
  - Endpoint: POPF and/or death

- **Results**
  - No difference in POPF (20% vs 22%; P=0.84)
  - No difference in 90- or 120-day mortality (P=0.98, P=0.69)

- **Conclusions**
  - There is no difference between stapler vs hand-sewn closure for distal pancreatectomy
Routine Intraperitoneal Drainage, Yes, No, Maybe?

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>P</strong></td>
<td>357 patients - Whipple and distal pancreatectomy</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>NO INTRAPERITONEAL DRAINAGE</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>INTRAPERITONEAL DRAINAGE</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>NO DIFFERENCE OF COMPLICATIONS (MORBIDITY AND MORTALITY – 90 days)</td>
</tr>
</tbody>
</table>

Prospective multicenter trial
9 high volume centers (∼50 PD/yr)
90 days follow up

CONCLUSION:

- Elimination of intraperitoneal drainage in all cases of PD increases a 4-fold increase in mortality from 3% to 12%.

- Elimination of the drain may directly increase mortality.
Postoperative Care: Octreotide no benefit in fistula incidence

**Octreotide**
- 4 RCT from Europe showed significant decreases in overall complication rates
  - 2/4 reported significantly lower rates of POPF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowy et al. (MDACC)</td>
<td>PD: Octreotide vs no octreotide x 5 days</td>
<td>120</td>
<td>No significant difference in complications, including POPF</td>
</tr>
<tr>
<td>Yeo et al. (Hopkins)</td>
<td>PD: Octreotide vs no octreotide x 7 days</td>
<td>211</td>
<td>No significant difference in complications, including POPF</td>
</tr>
</tbody>
</table>

- SOM trial (Allen et al.)

**Nutrition**
- Postoperative TPN started on day 1 until $\geq 1000$ kCal
- Not beneficial and was associated with higher rate of major complications (intraabdominal abscess)

**Conclusions**
- No proven benefit with octreotide
- Postoperative TPN is not associated with reduced morbidity

Perioperative: Pasireotide Reduces Post op Fistulas

**P** 300 patients
  - Undergoing either Whipple or distal pancreatectomy

**I** 900mcg subcutaneous pasireotide (152 patients) BID

**C** Placebo (148 patients)

**O** Primary: Pancreatic fistula, leak, or abscess requiring drainage (grade 3 or higher) at 60 days

Secondary:
  - Overall rate of pancreatic complications (all grades)
  - Rate of grade B or C fistula

Pancreatic Cancer Surgery

**Pasireotide Reduces Post op Fistulas: Study Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pasireotide (N=152)</th>
<th>Placebo (N=148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>82 (53.9)</td>
<td>83 (56.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Age — yr</td>
<td>64±11</td>
<td>64±13</td>
<td>0.78</td>
</tr>
<tr>
<td>Duct dilated — no. (%)</td>
<td>63 (41.4)</td>
<td>73 (49.3)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft gland — no. (%)</td>
<td>81 (53.3)</td>
<td>77 (52.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Pancreaticoduodenectomy — no. (%)</td>
<td>111 (73.0)</td>
<td>109 (73.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Distal pancreatectomy — no. (%)</td>
<td>41 (27.0)</td>
<td>39 (26.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Surgical placement of drain — no. (%)</td>
<td>43 (28.3)</td>
<td>36 (24.3)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma — no. (%)</td>
<td>77 (50.7)</td>
<td>77 (52.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>Postoperative maximum serum amylase — U/liter</td>
<td>230±294</td>
<td>230±312</td>
<td>0.95</td>
</tr>
<tr>
<td>Postoperative maximum serum glucose — mg/dl§</td>
<td>258±70</td>
<td>215±67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to bowel function — days</td>
<td>4±1</td>
<td>4±2</td>
<td>0.32</td>
</tr>
<tr>
<td>Length of stay — days¶</td>
<td>8±4</td>
<td>9±7</td>
<td>0.15</td>
</tr>
<tr>
<td>Patients who underwent pancreatectoduodenectomy</td>
<td>9±5</td>
<td>10±8</td>
<td>0.36</td>
</tr>
<tr>
<td>Patients who underwent distal pancreatectomy</td>
<td>6±1</td>
<td>7±2</td>
<td>0.02</td>
</tr>
<tr>
<td>All 14 doses received — no. (%)</td>
<td>115 (75.7)</td>
<td>128 (86.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Readmission — no. (%)</td>
<td>26 (17.1)</td>
<td>43 (29.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Pasireotide reduces postoperative fistulas in patients with pancreatic cancer. Significance noted for postoperative maximum serum glucose and all 14 doses received.*

**Hyperglycemia**

*Hyperglycemia is noted as a significant factor in the study groups.*
Primary endpoint:
Grade 3 Fistula
- Pasireotide 9.2%
- Placebo 20.9%
- Relative risk 0.44

Secondary Endpoints:
Pancreas Complications
- Pasireotide 7.9%
- Placebo 16.9%

Figure 2. Percentage of Patients with Grade 3 or Higher Pancreatic Fistula, Leak, or Abscess.

Chemical Splanchnicectomy

• **Design**
  - Patients with histologically confirmed, unresectable pancreatic adenocarcinoma randomized to intraoperative chemical splanchnicectomy with 50% alcohol vs placebo
  - Single institution, 137 patients
  - Endpoint: Pain scores

• **Results**
  - Significant reduction in mean pain scores at 2, 4, and 6 mo
    - Significant reduction, delay, or prevention of subsequent onset of pain
  - Significant improvement in survival in patients with significant preoperative pain

• **Conclusions**
  - Celiac plexus block in patients with unresectable pancreatic adenocarcinoma improves pain control and survival, particularly in patients with preoperative pain


City of Hope
Prophylactic Gastrojejunostomy

• **Design**
  - Patients with histologically confirmed, unresectable periampullary carcinoma and who were thought to **not be** at significant risk of GOO, randomized to retrocolic GJ vs no GJ
  - Single institution, 87 patients
  - Endpoint: Short-term perioperative morbidity and mortality, late development of GOO requiring intervention

• **Results**
  - No difference in short-term morbidity or mortality or in mean survival (8.3 mo in both groups)
  - Significantly greater incidence of late GOO in the group with no GJ (19% vs 0%; P<0.01; 8 of 43 patients)
    - All required intervention

• **Conclusions**
  - Prophylactic gastrojejunostomy significantly reduces the incidence of late GOO
  - Routine GJ should be performed when patient undergoing surgical palliation for unresectable periampullary carcinoma
  - *Low numbers of patients ultimately developed late GOO*

City of Hope

Lap GJ vs Duodenal Stent

• **Design**
  - Patients with malignant GOO randomized to laparoscopic GJ (LGJ) vs duodenal stenting (DS)
  - Single institution, 27 patients (13 with LGJ; 10 with DS)
  - Endpoint: Short term morbidity, hospital LOS, pain score, SF-36

• **Results**
  - No difference in survival
  - LGJ
    - Greater number of complications
    - Significant increase in LOS (11.4 vs 5.2 days, P = 0.02)
  - Improved QOL with DS

• **Conclusions**
  - In practice, prophylactic GJ should not be performed
  - However, when GOO present, duodenal stenting is preferred
**Palliative Biliary Stenting vs Surgery**

- **Overview**
  - 4 RCT and 1 Cochrane Metaanalysis
  - Patients with obstructive jaundice due to malignant obstruction of the distal common bile duct who require palliative decompression

- **Results**
  - No difference in technical or therapeutic success
  - Fewer complications with stent
  - More re-occlusions with stent
    - More readmissions with stent
    - Fewer total hospital days with stent
  - Lower procedure-related mortality with stent
  - No difference in overall survival
  - Great QOL scores with stent (P=0.042)
  - Lower total cost with stent (initial care + subsequent interventions; P=0.0013)

**Conclusions:** STENTING PREFERRED

Artifon et al. Am J Gastroenterol 2006;101:2031-37
Moss et al. Cochrane Database Syst Rev 2006;19
Randomized Trials that Work to Answer SOME important SURGICAL questions: SUMMARY

- Surgery versus chemoradiation: Surgical resection is the treatment of choice
- Techniques
  - PPPD vs standard PD: No significant difference
  - Extended lymphadenectomy vs standard PD: No significant difference
  - Pancreaticoenteric anastomosis: Similar morbidity and mortality
- Surgery in the setting of unresectable disease
  - Celiac plexus block: Reduced pain, improved survival
  - Treatment of GOO: Duodenal stent
  - Treatment of biliary obstruction: Biliary stent
    - But no RCT re: intraoperative decision to bypass vs stent
- Postoperative management
  - Postoperative drainage: Drainage associated with lower mortality
  - Octreotide: No significant difference in POPF
Adjuvant Therapy Options and Survival Benefit

- 2004 ESPAC-1: 5-FU vs CRT vs BOTH
- 2007 CONKO-001: Gemcitabine v Obs
- 2010 ESPAC-3: Gemcitabine vs 5-FU
- 2017 ESPAC-4: Gemcitabine+Capecitabine vs 5-FU
- 2018 PRODIGE 24: mFOLFIRINOX vs Gemcitabine
ESPAC-1: 5FU vs 5-FU+40 Gy vs BOTH

- 289 pts with resectable pancreatic ductal adenocarcinoma, includes patients with (+) margins
- 2x2 Factorial design
  - 5-FU alone (75), chemoradiation (40 Gy + 5-FU) (73), or both (72)
- Observation
  - Primary – 2 year OS
  - Secondary –
    - AE
    - QOL
    - Recurrence

Neoptolemos et al. NEJM, 2004
**ESPAC-1: 5 FU alone better than any chemoradiation**

- **Median Survival**
  - Chemoradiotherapy (overall)
    - 15.9 vs 17.9 months
  - Chemotherapy (overall)
    - 20.1 vs 15.5 months
  - Both
    - 19.9 months
  - Observation
    - 16.9 months

- **Recurrence**
  - 54% (158/289)
    - 35% locally
    - 34% distally
    - 27% both
  - Chemoradiotherapy
    - 82 vs 70%
  - Chemotherapy
    - 72 vs 81%

- **QOL – No differences**

*Neoptolemos et al. NEJM, 2004*
CONKO-001 Trial: Gemcitabine vs Observation

P  368 patients with gross complete (R0/R1) resection of pancreatic cancer and no prior radiation or chemotherapy

I  Adjuvant chemotherapy with 6 cycles of gemcitabine

C  Observation

O  Primary: Disease-free survival
   Secondary: Overall survival, toxicity, and quality of life
CONKO-001 Trial—Long-term follow up (JAMA, 2013)
Gemcitabine vs Observation

DFS: 13.4 vs 6.7
OS: 22.8 vs 20.8 months
Pancreatic Cancer: Adjuvant Therapy

ESPAC-3: 5FU+Folinic Acid vs Gemcitabine

P 1088 pts with resected pancreatic cancer:
- 159 centers: Europe
- Complete resection R0 or R1
- no malignant ascites, peritoneal or extraperitoneal mets,
I fluorouracil plus folinic acid (folinic acid, 20 mg/m2, intravenous bolus injection, followed by fluorouracil, 425 mg/m2 IV bolus injection given 1-5 days q 28 days)
C gemcitabine (1000mg/m2 IV infusion once a week for 3 of q 4 weeks)
O 1. Overall Survival
   2. Toxicity, PFS, global QOL

Neoptolemos, JAMA 2010
ESPAC-3: No Difference 5FU/Folinic Acid vs Gemcitabine

- OS 23 mo vs 23.6 mo
- PFS 14.1 vs 14.3 mo
- Predictors: grade, N stage, post op Ca 19-9, PS, smoking
- Resection margin not significant on MV

Neoptolemos, JAMA 2010
Pancreatic Cancer: Adjuvant Therapy

**ESPAC-4: Gemcitabine vs Gem/Capecitabine**

- **P** 730 pts with resected pancreatic and randomized <12 wks
- **I** 364 Gemcitabine six 4 week cycles
- **C** 366 Gemcitabine six 4 week cycles + Oral Capecitabine
- **O** 1. Overall Survival
  2. Toxicity
  3. Recurrence-free Survival
  4. 2 and 5 year survival
  5. Quality of Life
ESPAC-4: Gemcitabine vs Gem/Capecitabine

P 730 pts with resected pancreatic and randomized <12 wks
I 364 Gemcitabine six 4 week cycles
C 366 Gemcitabine six 4 week cycles + Oral Capecitabine
O 1. Overall Survival
   2. Toxicity
   3. Recurrence-free Survival
   4. 2 and 5 year survival
   5. Quality of Life
ESPAC-4: Gemcitabine 25.5 mo vs Gem/Capecitabine 28.0 mo

Margin (–) OS: 39.5 months!!

Neoptolemos et al. JCO Abstract 2016
PRODGE 24/CCCTG PA.6: mFOLFRINOX vs Gemcitabine

**P:** resected pancreas cancer n=493

**I:** mFOLFRINOX n=247

**C:** Gemcitabine n=246

**O:** OS

* mFOLFRINOX: 54.4 mo!!!!!
* Gemcitabine: 35.0 mo
P: metastatic pancreas cancer  
n=342

I: FOLFIRINOX  
n=171

C: Gemcitabine  
n=171

O: OS
- Gemcitabine: 6.8 mo
- FOLFIRINOX: 11.1 mo

Conroy NEJM 2011
Pancreatic Cancer-Metastatic Disease

Gemcitabine+nab-Paclitaxel: OS 8.5 MONTHS

P: metastatic pancreas cancer
   n=861

I: gemcitabine +nab-palictaxel
   n=431

C: Gemcitabine n=430

O: OS
   Gemcitabine: 6.7 mo
   Gem/nab-paclitaxel 8.5 mo

Van Hoff NEJM 2013
Summary

• Diagnosis: CT/MR/EUS
• Treat: Discuss and collaborate with surgery prior to instrumentation and determining resectability
• Continue MIS approaches and minimize morbidity
• Adjuvant: minimize toxicity and optimize survival
  – Gemcitabine and Capecitabine: 28.0 median survival (margin negative: 39.5 months)
  – mFOLFIRINOX: 54 months survival
• Metastatic Disease:
  – Gemcitabine
  – Gemcitabine + nab-paclitaxel: 8.6 months OS
  – FOLFIRINOX: 11.1 months OS
Patients with stage IV pancreatic cancer who have been placed in best possible response with first line chemotherapy defined as:

1. Must have obtained a best response of at least stable disease (SD) or partial response (PR) for a period of 2 months with no further shrinkage of > 20% on scan

Randomized

Pembrolizumab (200 mg q 3 weeks*) + paricalcitol (25 mcg 3 times per week**)

Pembrolizumab (200 mg q 3 weeks*) + placebo**

Biopsy 0 9 wks 6 mos

CA19-9 (or CEA or CA-125 for not expressers of CA19-9) q 3 weeks
CT scan q 9 weeks

* Pembrolizumab: 200 mg infused q 3 weeks, on day 1 of each 21-day cycle

**Paricalcitol: 25 mcg IV (or for placebo, equivalent volume) 3 times per week (given on day 1 prior to Pembrolizumab) and days 3, 5, 8, 10, 12, 15, 17, and 19 (±1 day allowed for dosing of each 21-day cycle)

Refer to Section 5 for the detailed Trial Schedule
MORPHEUS PDAC Study Design –1L Cohort (Wave 2)

1L Met PDAC

Screening → Stage 1

1L Met PDAC

Entry Biopsy → Preliminary n=15 → Expansion n=25

Atezo + Gem/Abx + CD40

Atezo + Gem/Abx + CD40 + Bev*

Atezo + Gem/Abx + Bev

Atezo + Gem/Abx + CSF1R

PD Biopsy

Gem/Abraxane**

* Open after safety evaluation completed for Atezo+Gem/Abx+CD40

** Patients with PD on 1L cohort control arm (Gem/Abraxane) will have the option to enroll to 2L cohort (if meeting eligibility criteria and signing ICF)
MORPHEUS PDAC Study Design – 2L Cohort (Wave 1 and Wave 2)

Screening → Stage 1 → Stage 2

- 2L Met PDAC
  - Entry Biopsy
  - Preliminary n=15
  - Expansion n=25

- Atezo + Cobi*
- Atezo + PEGPH20 (n=40)
- Atezo + BL8040
- Atezo + FAP-IL2v Q2W *
- Atezo + FAP-IL2v Q3W *
- Atezo + CSF1R
- FOLFOX or Gem/Abraxane

- PD / Re-Entry Biopsy
- Atezo + Cobi
- Atezo + FAP-IL2v

* Patients from Atezo + Cobi arm will not be eligible to go to stage 2 “Atezo + Cobi”. Patients from Atezo + FAP-IL2v arm will not be eligible to go to stage 2 “Atezo + FAP-IL2v”

Wave 1 arms: may have finished enrollment
Wave 2 arms

Confidential
Novel denatured amino acid, D,L-alpha-metyrosine

• The denatured tyrosine is believed to disrupt cancer’s protein synthesis process and cause a breakdown of cancer cell defenses and regulatory proteins.

With microdoses of sirolimus, methoxsalen and phenytoin.

• 1) increase absorption of the tyrosine into the tumor environment through increased cellular ketosis (sirolimus)
• 2) increase the production of reactive lipid species (phenytoin)
• 3) enhance the effect of oxidative stress inside the cancer cell (methoxsalen)

• No limit to number of prior regimens
• PK’s, Patient reported outcomes, CTC will be collected
• MSI-H pancreatic cancer need to receive pembrolizumab before considering this protocol
• Any patients with dysphagia, odynophagia, esophageal dysmotility or stricture, known GI malabsorption syndrome, or intractable diarrhea that may significantly alter the absorption of any of the components of SM-88, e.g., cirrhosis are excluded

• Testing 2 dose levels
• D,L-alpha-metyrosine 460 mg or 920 mg
Pancreas Cancer Clinical Trials at COH

Metastatic 1<sup>st</sup> line: Maintenance

IRB # 17363 A SU2C Catalyst Randomized Phase II Trial of the PD1 Inhibitor Pembrolizumab (Keytruda) With or Without a Vitamin D Receptor Agonist Paricalcitol (Zemplar) in Patients With Stage IV Pancreatic Cancer Who Have Been Placed in Best Possible Response (With no Further Improvement in Their Tumor)

Metastatic 2<sup>nd</sup> line +:

IRB #18141 A Phase II Multi-Center Study of SM-88 in Subjects with Pancreatic Cancer Whose Disease Has Progressed or Recurred after/on First Line Chemotherapy (any line after first line – requires 28 day washout)

Morpheus Trial – Anticipate opening within a couple of weeks
Metastatic 1<sup>st</sup> line, 2<sup>nd</sup> line and 3<sup>rd</sup> line treatment
Thank you

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